Review

MOLECULAR METABOLISM

Primary prevention of beta-cell autoimmunity and type 1 diabetes — The Global Platform for the Prevention of Autoimmune Diabetes (GPPAD) perspectives

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ABSTRACT

Objective: Type 1 diabetes can be identified by the presence of beta-cell autoantibodies that often arise in the first few years of life. The purpose of this perspective is to present the case for primary prevention of beta-cell autoimmunity and to provide a study design for its implementation in Europe.

Methods: We examined and summarized recruitment strategies, enrollment rates, and outcomes in published TRIGR, FINDIA and BABYDIET primary prevention trials, and the TEDDY intensive observational study. A proposal for a recruitment and implementation strategy to perform a phase II/III primary prevention randomized controlled trial in infants with genetic risk for developing beta-cell autoimmunity is outlined.

Results: Infants with a family history of type 1 diabetes (TRIGR, BABYDIET, TEDDY) and infants younger than age 3 months from the general population (FINDIA, TEDDY) were enrolled into these studies. All studies used HLA genotyping as part of their eligibility criteria. Predicted beta-cell autoimmunity risk in the eligible infants ranged from 3% (FINDIA, TEDDY general population) up to 12% (TRIGR, BABYDIET). Amongst eligible infants, participation was between 38% (TEDDY general population) and 97% (FINDIA). Outcomes, defined as multiple beta-cell autoantibodies, were consistent with predicted risks. We subsequently modeled recruitment into a randomized controlled trial (RCT) that could assess the efficacy of oral insulin treatment as adapted from the Pre-POINT pilot trial. The RCT would recruit infants with and without a first-degree family history of type 1 diabetes and be based on general population genetic risk testing. HLA genotyping and, for the general population, genotyping at additional type 1 diabetes susceptibility SNPs would be used to identify children with around 10% risk of beta-cell autoimmunity. The proposed RCT would have 80% power to detect a 50% reduction in multiple beta-cell autoantibodies by age 4 years at a two-tailed alpha of 0.05, and would randomize around 1160 infants to oral insulin or placebo arms in order to fulfill this. It is estimated that recruitment would require testing of between 400,000 and 500,000 newborns or infants.

Conclusion: It is timely and feasible to establish a platform for primary prevention trials for type 1 diabetes in Europe. This multi-site European infrastructure would perform RCTs, supply data coordination and biorepository, provide cohorts for mechanistic and observational studies, and increase awareness for autoimmune diabetes.

Keywords Type 1 diabetes; Beta-cell autoimmunity; Prevention; Antigen-based immunotherapy

1. INTRODUCTION

Type 1 diabetes results from an autoimmune destruction of the insulin-producing beta cells within the pancreatic islets of Langerhans. This process is identified by circulating islet autoantibodies to beta-cell antigens and is mediated by a lack of immunological self-tolerance [1,2]. Self-tolerance is achieved by T cell exposure to self-antigens in the thymus or in the periphery (i.e. outside the thymus or bone marrow, in secondary lymphoid tissues such as lymph node, gut and spleen) in a manner that deletes autoreactive effector T cells or induces

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regulatory T cells and regulatory cytokines such as interleukin-10 (IL-10). Immunological tolerance can be achieved by administration of antigen under appropriate conditions [3,4]. Evidence is now emerging in humans that these approaches may be effective in chronic inflammatory diseases such as multiple sclerosis, allergy, and type 1 diabetes [5–8].

GPPAD is the **G**lobal **P**latform for the **P**revention of **A**utoimmune **D**iabetes that was established in 2015 in Germany and UK with the intention to establish an infrastructure for primary prevention trials. More specifically, we aim to develop and launch the first randomized controlled phase II/III trial (RCT) using autoantigen-based therapy and to consider other approaches that might inhibit or prevent the earliest events in newborns that lead to multiple anti-islet autoantibodies. GPPAD will also investigate the feasibility, practicalities, and acceptability of recruitment of newborn children into mechanistic studies and third generation natural history studies. Antigen-based therapy in type 1 diabetes will serve as a model system. However, the planned platform will be adaptable and deployable in the investigation and prevention of other approaches to type 1 diabetes primary prevention, and to other childhood conditions and illnesses, with a major underlying goal of the promotion of better health outcomes early in life and during pregnancy based on improved understanding of the human immune system. GPPAD will focus on primary prevention, defined as the prevention of seroconversion to beta-cell autoantibodies. Primary prevention has a strong rationale. First, neonates who are at increased risk to develop multiple beta-cell autoantibodies and type 1 diabetes can be identified using family history and/or genetic markers at several loci, in particular HLA class II and class I haplotypes. Second, there is a marked peak incidence period of beta-cell autoantibody seroconversion between age 9 months and 2.5 years, providing a finite study follow-up until age 3–4 years and the primary endpoint in a RCT. Third, there is an early autoantibody target, insulin and its precursor preproinsulin, encoded by a gene with a common polymorphism that confers genetic risk for type 1 diabetes by altering neonatal immune tolerance to insulin and its precursors. Primary prevention also offers the opportunity and a platform to have a second chance at prevention (secondary) if children develop beta-cell autoantibodies.

It is widely held that if neonatal tolerance to beta-cell antigens could be enhanced, this could prevent or delay the onset of pre- or asymptomatic type 1 diabetes (defined as loss of tolerance and multiple autoantibodies) and prevent or delay disease diagnosis. The key here is "neonatal", the time when the natural mechanisms of immune tolerance are fully active as the child becomes tolerant to commensal microorganisms and dietary components. Currently, antigen-specific tolerance approaches are attempted in individuals in whom the immune system has matured and in whom an autoimmune memory response is well established. We, however, have laid the foundation for antigen-specific primary prevention by demonstrating in genetically at-risk children aged 2–7 years who are beta-cell autoantibody negative that orally-delivered insulin is safe (does not affect plasma glucose levels) at a dose that appears to engage the immune system in a manner that is consistent with immune-mediated, tolerogenic protection [9].

Hence, we believe that we have three important pillars for primary prevention to move forward – a strategy to identify neonates at type 1 diabetes risk by genetic markers; knowledge when beta-cell autoimmunity starts; and demonstration that antigen-specific therapy is feasible. With these in hand, the task is to develop an infrastructure that can make a significant impact on reducing the numbers of children who develop type 1 diabetes via broad and safe primary prevention therapy. Avenues to achieve the implementation of such a program will be discussed.

2. REVIEW OF PREVIOUS PRIMARY PREVENTION EFFORTS

2.1. The TRIGR study (Trial to Reduce IDDM in Genetically at Risk)

The TRIGR study is a dietary randomized controlled trial aiming to reduce the incidence of beta-cell autoimmunity and type 1 diabetes by weaning to an extensively hydrolyzed formula [10]. The trial was unsuccessful in reducing beta-cell autoimmunity. The study is still ongoing to access risk of type 1 diabetes. It has estimated a cumulative incidence of 9.9% by age 6 years for multiple beta-cell autoantibodies in the control group. The study was powered to detect a 35% change in the end point, and 20% risk to miss a true difference between the groups. Concurring with initial estimates, the risk of positivity for two or more beta-cell autoantibodies was 11.4% (95%CI, 9.4%–13.2%) among those randomized to the control group (conventional formula, $n = 117$), and similarly 13.4% (95%CI, 11.3%–15.5%) among those randomized to the casein hydrolyzate formula ($n = 139$). There were no clinically significant differences in the rate of reported adverse events between the two groups.

Although the outcome of TRIGR was disappointing from an efficacy viewpoint, the TRIGR study has without doubt an unprecedented value in uniquely demonstrating that conducting primary prevention trials for type 1 diabetes is feasible. TRIGR has recruited 2159 infants with HLA-conferred disease susceptibility[10] and a first-degree relative with type 1 diabetes of a total of 5156 (42%) tested for HLA eligibility. Infants were prospectively followed for at least 6 years with high retention and documented protocol adherence.

2.2. The BABYDIET pilot study

The open randomized controlled BABYDIET study aimed to reduce beta-cell autoimmunity by delayed gluten exposure in the first year of life [11]. Evidence came from two natural history studies, BABYDIAB and the Diabetes and Autoimmunity Study in the Young (DAISY), which demonstrated that early gluten exposure is associated with increased risk of beta-cell autoimmunity in childhood [12,13]. Of 1168 newborn children with a first-degree relative with type 1 diabetes screened for eligibility, 169 were found eligible because they had the high risk HLA genotypes[11], and 150 (89%) consented to participate. Participants were followed for at least 3 years with 27 children developing beta-cell autoantibodies (cumulative risk by age 4 years for any beta-cell autoantibody: 15.4% (95%CI, 9.5%–21.3%); for multiple beta-cell autoantibodies: 9.5% (95%CI, 4.6%–14.1%). The study demonstrated no beneficial effect of delaying gluten exposure to 12 months of age when compared to introducing gluten at 6 months of age in the intention to treat as well as per protocol analysis. Only 70% of families adhered to the dietary-intervention protocol while 30% introduced gluten earlier or later than recommended. This study indicates that an open dietary prevention trial is likely to have limitations with respect to protocol adherence, which in consequence will affect the ability to measure efficacy of the intervention.

[10] DQB1*02/DQB1*03:02; DQB1*03: 02/x (x not DQB1*02, DQB1*03:01, or DQB1*06:02); DQA1*05-DQB1*02/y (y not DQA1*02:01-DQB1*02, DQB1*03:01, DQB1*06:02, or DQB1*06:03); DQA1*03-DQB1*02/y (y not DQA1*02:01-DQB1*02, DQB1*03:01, DQB1*06:02, or DQB1*06:03).

[11] DRB1*03-DQA1*0501-DQB1*0201/DRB1*04-DQA1*0301-DQB1*0302;DRB1*04-DQA1*0301-DQB1*0302/DRB1*04-DQA1*0301-DQB1*0302;DRB1*03-DQA1*0501-DQB1*0201/DRB1*03-DQA1*0501-DQB1*0201;DRB1*04-DQA1*0301-DQB1*0302/DRB1*08-DQA1*0401-DQB1*0402;DRB1*04-DQA1*0301-DQB1*0302/DRB1*01-DQA1*0101 -DQB1*0501.

